HEINEMAN (H.N.) With Compliments of the Author.

INDICAN IN HEALTH AND DISEASE

BY

H. N. HEINEMAN, M. D.

ASSISTANT TO LABORATORY OF THE ALUMNI ASSOCIATION OF THE COLLEGE OF PHYSICIANS AND SURGEONS, N. Y.

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INDICAN IN HEALTH AND DISEASE.

INDICAN is a normal organic constituent of the urine. Schunck in 1857 first called attention to it and proved it to be a compound body.

Composition.—It is composed of indigo-blue, indigo-red, indigglucin, leucine and acids. The first two are coloring matters, of which the former is identical with Heller's uroglaucin, and the latter with Berzelius' urrhodin.

Indican has been separated from the urine in the form of small branching white shining masses by Bauman and Brieger,* who have determined its chemical formula to be $C_8H_6NSO_4K$. They consider it to be the combination of the ether sulphate of indol-hydroxyl with an alkali, and have proposed the name of indoxyl sulphate. It ranks among the aromatic series of compounds to which phenol and benzol belong.

Source of Indican.—Jaffe, Kuhne, Salkowski and others have demonstrated that indican is derived from a nitrogenous substance called indol. Indol appears in the intestines and is also found in the fæces, the peculiar odor of the latter being due to its presence. Kuhne proved that it is a product of the decomposition of albuminous substances acted upon in the intestine by the pancreatic juices.

* *Zeitschrift f. Phys. Chemie*, iii, p. 254.

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Brieger * succeeded in obtaining it, without the body, from the simple decomposition of the liver of the horse, maintained at a temperature of 40°, and with a feeble alkaline reaction. It is absorbed from the small intestine and eliminated by the kidneys under the form of the conjugated compound indican. Indol as well as its derivative indican, both belong as we have already stated, to the class of aromatic substances.

Among the experiments (of which those of Christiani † are the most recent) to prove the relation of indol and indican, has been the introduction of the former substance, by hypodermic injection and otherwise, into the lower animals, when invariably an increase in the excretion of indican followed. Other substances chemically allied to indol, have also been similarly used and have produced some increase in indican, but this was never so pronounced as when indol itself was employed.

Among the latter substances may be mentioned phenol, benzol (Christiani and others), creosote and bitter almonds (Kletzinsky). The first of these is also normally found in the intestine, produced in the same manner as indol, and it reappears in the urine to some extent, whether artificially injected or absorbed from the intestine, under its own form.

Recently Ewald ‡ in a case of artificial anus, after withdrawing the secretions from the upper portion of the small intestine found that neither indican nor phenol appeared in the urine. When the secretions were permitted to pass through the intestine, both substances were present. This experiment he claims further demonstrates both the derivation of indican from indol, and also that indol is produced in the lower portion of the small intestine only.

In opposition to what would naturally be supposed, in

* *Zeitschrift f. Phys. Chemie*, iii, p. 134.

† *Ibid*, ii, p. 272.

‡ *Virchow's Archiv*, lxxvii, p. 409.

the herbivora in which indican is largely (Jaffe) present in the urine, Brieger* found phenol and indol always in small quantities and present in the rectum and fæces only, and not in the contents of the intestine.

Christiani and other investigators of whom mention has already been made, have demonstrated that even after a prolonged exclusive meat diet, indican was excreted and in increased quantity.

Other sources than indol, and organs other than the kidneys for the production of indican suggest themselves. The blood, from which all other coloring matters of the body are derived, may yet prove to be an additional source of the coloring matter, indican. A coincidence which is so striking that it cannot be considered as accidental, would tend to confirm this possibility. Thus many diseases,† which are attended by a diminution of the quantity of hæmoglobin of the blood, furnish a corresponding increase in the amount of indican. And in some diseases, such as pleurisy and peritonitis, the diminution of the first at a particular stage, coincides exactly with the period of time when indican is generally found in greatest abundance. Hippuric acid, a substance which Jaffe has suggested may be derived from the same material as indican, with which it is frequently (Jaffe, Senator) found associated, is formed in other tissues besides the kidneys, according to the recent experiments of Salomon.‡ Further experiment may likewise demonstrate other tissues of the body as the seat of formation of indican.

Color.—Indican does not impart any color to the urine, by which its presence can always be predetermined. In rare instances, owing to its decomposition by a ferment either before or after being voided from the bladder, it

* l. c.

† See Quinquand's article, ARCHIVES OF MEDICINE, vol. iii, No. 1, p. 32, 1880.

‡ *Zeitschrift f. Phys. Chemie*, iii, p. 366.

gives to the urine a blue tint. In such cases, which I have met with, crystals of indigo-blue are precipitated. These are very small blue needle-shaped crystals, usually aggregated and forming radiated masses, and have no action upon polarized light.

We must carefully distinguish by microscopic examination the blue color sometimes given to urine by the presence of a fungus.

It is stated by Neubauer and Vogel* that urine containing indican is very generally yellow in color. In 255 examinations I have noted the color when indican was present. Of these

101 specimens had a decidedly yellow tint,

64 were dark amber,

57 pale or straw colored, and

33 pale amber.

The aggregate of the other colors preponderated, though, as will be seen, there was a predominance of the yellow over any one other color.

Tests.—Owing to the readiness with which indican is decomposed by the mineral acids, its recognition is made quite easy.

The determination of the amount of indican is deduced from the quantity of indigo-blue which is set free. It has been well established by Hoppe-Seyler, by means of spectroscopic examination, that the indigo-blue always bears a definite ratio to the quantity of indican. The amount of indigo-blue is judged simply by the intensity of the blue color imparted to the menstruum by which it is dissolved. Generally it is the depth of color of the chloroform, this being the general solvent employed.

Jaffe, Salkowski and Senator have each in succession made some improvements in the tests employed. Hennige has added a few suggestions, and I have some to make.

* Analysis of the Urine, last edition, p. 67, N. Y., 1879.

Senator's Test.—Pour 10 cc. of urine into a deposit glass and add slowly, while briskly stirring the mixture, 10 cc. of pure hydrochloric acid. In the course of a few minutes, sometimes longer, the mixture acquires a violet or bluish tint, according to the amount of indican present, and fine flocculi of indigo-blue may be seen to be precipitated. Next add drop by drop a few drops of a saturated solution of calcium hypochlorite, which causes still further decomposition of the indican and increases the depth of color of the mixture. The calcium solution is added until we have obtained what we suppose the bluest tint, generally alone determined by the fact that the mixture begins to lose color when we have added a trifle too much. Next we add a small quantity of chloroform, agitate it with the mixture, this will dissolve all the indigo-blue which has been set free, carry it down with it to the bottom of the glass, and leave the indigo-red in the mixture above. We now pour off the supernatant liquid, leaving the chloroform with its dingy blue color behind. By passing the chloroform, according to the suggestion of Hennige, through torn bits of fine filtering paper, we have left a clear blue solution.

Weber's Test.—"W. Weber* employs a method of detecting indican, which is especially valuable in those cases in which the quantity present is very small. To 30 cc. of urine in a large test-tube add an equal volume of concent. hydrochloric acid, and warm the mixture. One or two drops of nitric acid increase the sensitiveness of the test. The mixture is then cooled by holding it in running water. A layer of ether, 2 or 3 cc., is poured upon it, and the mixture shaken. Add a few drops of alcohol if the blue color is not evident in a few minutes. After a while the indigo-blue separates from the ether and forms a deposit between the two fluids, while the indigo-red remains dissolved in the ether."

* *Archiv der Pharmacie*, Oct., 1878, p. 340. *Bost. Med. and Surg. Journal*, 1879.

Modification of Senator's test.—I have obtained more accurate results and avoided the necessity of repeating examinations, by the following suggestions:

First. Add the chloroform after the acid has been added. Subsequently add the solution of calcium hypochlorite, and after each drop agitate and allow the chloroform to settle so as to recognize its color.

In this way, even if the mixture should begin to fade from having added a drop too much of the calcium solution, we have only to remember the depth of color which the chloroform had acquired just previous.

A ready test for the ordinary practitioner, and which, while it will not indicate the presence of small quantities, will show any increase, is found in the following. The faintest blue tint here represents a slight increase.

Fill a good-sized ordinary test-tube one-third full of urine, add equal amount of hydrochloric acid (c. p.) slowly and with constant shaking, warm slightly and then cool, when the specimen assumes the violet or bluish tint. Next add from 30–60 drops (according to size of tube) of chloroform, and after shaking the mixture thoroughly, allow it to settle and observe the color of the chloroform. Now add drop by drop a dilute solution of calc. hypochlor., agitating and continuing until the chloroform has acquired its deepest blue tint.

Remarks upon the tests.—1. Dark and bile-stained urine should be first decolorized by plumbic acetate, not used in excess. Albumen must also be separated.

2. Decomposed urine must not be employed.

3. The resulting color of the chloroform sometimes varies from that described, a greenish black and red (the color of indigo-purpurin) being obtained. In all of these cases filtration through bibulous paper will invariably leave some tint of blue upon the filter, showing the presence of indigo-blue.

4. We have no means better than the judgment of the eye for determining the depth of color of the indigo-blue. Thus a deep blue indicates a marked increase, a very faint blue slight or normal, a decided blue a moderate increase. Scales of color, for comparison, have proven useless in the hands of Hennige and others.

5. The suggestion of Hoppe-Seyler that the degree of concentration of urine determines in a measure the reaction found, must be borne in mind.

Through the kindness of the resident staff of the Roosevelt, New York and Bellevue Hospitals, I have been enabled to examine upward of 200 cases, of which more than 150 were in cases of disease.

I have employed Senator's test with Hennige's suggestion of filtering the chloroform deposit. Weber's test has occasionally been made use of, simply as a means of comparison and to appreciate its delicacy. But the use of the large quantities of acid, which this latter requires, and the resulting atmosphere of chlorine in which the experimenter is placed, made it too obnoxious for constant use.

Each case has been examined at intervals, three or more times. Many specimens were repeatedly reëxamined in order to insure accuracy.

In reviewing the literature I find a serious cause for regret in the indefinite results and conclusions given by many investigators. Instead of stating with positiveness the exact number of cases seen and investigated, the terms, frequently, in several cases, in numerous instances, etc., are used. Still further the proportionate increase of indican, whether moderate or marked, is not always stated.

With the view of assisting future investigations I have arranged the appended table, which includes 396 cases investigated by Hoppe-Seyler (100 cases of normal urine), Senator, Hennige and myself. The results of the numer-

ous investigations and invaluable labors of Kuhne, Salkowski, Heller, Scherer, Virchow, Edlefsen, De Vries and others, I shall compare with the deductions to be made from the above table. In some instances, conclusions already arrived at have been corroborated, in others additional investigations have modified previous inferences.

First, in 149 cases of normal urine, of which Hoppe-Seyler investigated 100, indican was present in all but 14. Of 49 cases reported by me, in 21 there was an increase above the average normal amount, and in 9 a very marked increase.

Next, in diseased states :

Circulatory system.—Of 5 cases of cardiac disease 3 exhibited a normal amount, 2 a moderate and marked increase respectively. In one case of aneurism, indican was absent.

Respiratory system.—Of 6 cases of pleurisy, pneumonia and empyema, 2 had a normal quantity, 2 a moderate and 2 a marked increase. Senator states that in pneumonia and pleurisy he has found a moderate increase.

Of 13 cases of acute and chronic phthisis 2 showed marked, 3 moderate increase, 5 a normal or slight amount and 3 absence. Hennige states that the condition of the intestine, whether diarrhœa be present or not, determines the increase in phthisis. Senator, with whom I agree, states with or without diarrhœa there is a moderate or marked increase.

Digestive system.—In 3 cases of stomach dyspepsia and 1 of dilatation there was marked increase. In a few cases of ulcer of the stomach, Senator has met with moderate increase. In numerous cases (number not stated) of gastro-duodenitis, Hennige found very marked increase. In 1 case I have found absence of indican and in 3 marked increase. In 5 cases of diarrhœa, there was marked increase in all. Of 3 cases of dysentery, 2 exhibited a

slight amount and 1 none; of 4 cases of chronic constipation, 2 exhibited absence, 2 marked increase. Senator, and with him, Hennige, Jaffe, Edlefsen and DeVries, find that in simple constipation from atony, without invagination, only a slight amount of indican is present. The result in 2 cases met with by me is at variance with this. In 1 case of intussusception the increase was very marked. In 7 cases of peritonitis there was marked increase, and this was greatest in the acute cases and in those which were general rather than those that were localized. In 4 cases of intestinal hemorrhage there was marked increase. In 1 case of cholera morbus there was marked increase. Senator, Wyss and Gubler have found marked increase in this and in cases of Asiatic cholera.

Liver.—Of 9 cases of cirrhosis, 2 only exhibited a moderate and marked increase respectively, 2 were normal, and in 5 there was none.

Genito-urinary system: *Kidneys.*—Of 16 cases of Bright's disease, 10 presented a marked and 4 a moderate increase, in 2 indican was absent.

Senator states that he has found no increase in any except cases of atrophied granular kidney. Heller, Scherer and Virchow had previously reported increase in indican in kidney lesions other than the one just mentioned. My own cases confirm this latter view. Of 7 cases of Addison's disease, 3 had moderate and 4 marked increase.

Bladder and Urethra.—Of 12 cases in which pus was found in the urine in connection with urethral stricture, cystitis and gonorrhœa, 7 gave moderate and 1 marked increase, 3 normal or slight amount, and 1 none.

Uterus and Ovaries.—1 case of uterine disease had marked increase; 1 case of puerperal fever, normal or slight amount; in 2 cases of ovarian tumor none, and in 3 cases of pregnancy 1 had marked and 2 moderate increase.

Osseous system.—Of nine cases of arthritis, caries and necrosis, 4 had moderate increase, 3 normal or slight amount, and 4 none. Of 6 cases of suppuration and cellulitis unconnected with bone disease, 3 had moderate increase, 2 normal amount and 1 none.

Nervous system.—Indican was absent in 1 case of apoplexia meningea; markedly increased in 1 case of prog. muscular atrophy, in 1 case of insanity and epilepsy. In 3 cases of paraplegia, 2 had marked increase and 1 normal amount. In 1 case of sciatica, the quantity was normal. In 2 cases of cerebral tumor and 1 of hypochondriasis and nocturnal emissions there was absence. Several authorities claim that spinal irritation is generally accompanied by an increase of indican.

General diseases.—Of 5 cases of alcoholism, 2 had moderate and 1 marked increase and 2 were normal.

Of 20 cases of rheumatism, 8 of 10 cases of acute disease were normal, 1 had marked increase and 1 none. In 4 of 10 chronic cases the quantity was normal or slight, markedly increased in 4 and moderately in 2.

Of 19 cases of malaria, 6 were normal, 5 had moderate and 1 marked increase and 7 had none. Of 6 cases of typhoid fever, 1 had moderate and 5 marked increase. Hennige has found the increase in typhoid fever dependent upon the presence of diarrhœa. Senator and I have found it independent.

In 1 case of convalescence from yellow fever the quantity was normal. Of 10 cases of constitutional syphilis, 4 had moderate and 1 marked increase, 2 were normal, 3 had none.

Of 6 cases of chlorosis, 3 had moderate increase and 3 normal or slight amount. There was a normal or slight quantity in 2 cases of Werlhof's disease, marked increase in 1 case of progressive pernicious anæmia and absence in 1 case of leucocythæmia. In 3 cases of trichinosis and 2

of lead poisoning there was marked increase. In 1 of chronic arsenical poisoning, absence.

In 21 cases of carcinoma interna, there was very marked increase in 19 and absence in 2.

In 3 cases of abdominal lympho-sarcoma and in 1 case of osteo-sarcoma there was marked increase in all.

Conclusions.—Indican is only exceptionally absent in health. It may vary in quantity in the healthy individual, generally being small in amount, but occasionally as marked as in disease.

Certain diseased conditions tend to produce a decided increase.

The most marked increase is obtained in those diseases which affect the alimentary canal, and more especially the small intestine, whether they be local or general diseases with local lesion. Among these are dyspepsia, gastro-duodenitis, chronic constipation, intussusception, diarrhœa, peritonitis, cholera, lead poisoning and typhoid fever.

In diseases causing inanition, as phthisis and other prolonged suppurative diseases, as caries and necrosis, marked increase is found.

Among the diseases producing altered blood states, some, such as malaria, syphilis, rheumatism and alcoholism, progressive anæmia and chlorosis, although *always* causing the most profound blood-changes, *do not always* effect a decided increase. This is a singular exception, to which Senator has called attention, but the investigations are not yet sufficiently numerous to draw conclusions.

Certain nervous disorders, as insanity, epilepsy, Addison's disease, progressive muscular atrophy and paraplegia, cause marked increase.

Disordered function of the kidneys, as in chronic Bright's disease, causes marked increase.

Internal malignant tumors, as carcinomata and sarcomata, cause increase most markedly and constantly of all.

The explanation of the cause of the increase in various diseases is not as yet adequate to satisfy all cases.

The experiment of Jaffe of ligating the small intestine, by which the amount of indican excreted was increased, demonstrates that conditions retarding peristalsis and favoring the absorption of indol, cause an increase of indican. This reasonably explains the result in cases of peritonitis, constipation and similar disorders.

How, satisfactorily, to account for the result in other diseases must, I regret to state, still remain unanswered.

The theory of Hennige that other diseases act through the nervous system and produce a change in the nature of the pancreatic secretions, and thus cause an increase, is effectually answered by Senator. He calls attention to the fact that indol, the mother substance of indican, is a product of decomposition. Furthermore, Brieger has shown that indol is produced without the presence of pancreatic juices.

Possibly in changes in the circulating fluid, rather than in local disturbances of the system, we may find the reason for the increase in the remaining diseases.

	None		Normal or Slight		Moderate Increase			Marked Increase							Observers who have not reported exact statistics
	Hennige	Heineman	Hennige	Heineman	Hennige	Rosenstirn	Heineman	Hennige	Carter	Heineman	Salkowski	Rosenstirn	Hoppe-Seyler	Senator	
Normal		11		17			12			9					Schunck, Hoppe-Seyler, (100 *cases*) Senator, Carter
Cardiac Dis.				3			1			1					
Aneurism (Aorta)				1											
Ac. Pneumonia				1											
Pleurisy and Empyema				1			2			2					
Ac. Miliary Tuberculosis.			2								1				
Phthisis		3		3			3			1					Senator
Dyspepsia										3					
Dilatation of Stomach										1					
Gastro-duodenitis		1								3					
Diarrhœa								4		1					Senator
Dysentery		1		2											
Constipation chr.	2									2					
Intussusception									1						
Cholera Morbus								1							Gubler, Wyss, Senator
Peritonitis								5			2				Kletzinsky
Cirrhosis	5			2			1			1					
Jaundice			4												
Chr. Bright's Disease		2					4			6				4	Rosenstirn, Gubler, Kletzinsky
Stricture Urethræ				1			4			1					
Cystitis Vesicæ				2			3								
Dilatation Vesicæ		1													
Gonorrhœa							1								
Malaria	7			6			5			1					
Typhoid Fever							1			5					
Yellow Fever				1											
Syphilis		3		2			4			1					
Leucocythæmia		1													
Pern. Anæmia Prog.								1							Rosenstirn
Werlhof's Disease			2												
Chlorosis			3		3										Rosenstirn
Trichinosis								3							
Lead Poisoning								1		1					
Arsenical "			1												
Sarcoma of Thigh										1					
Carcinoma Interna		2						2	1	3			1	12	Neftel
Lympho-Sarcoma of Abdomen											1			2	
Pregnancy							2			1					
Uterine Disease										1					
Ovarian Tumor	2														
Puerperal Fever				1											
Arthritis					1										
Caries & Necrosis		2		3	2		1								
Goitre				1											
Apoplexia-Mening.	1														
Prog. Musc. Atphy								1							
Addison's Disease						3		1				3			
Insanity										1					
Epilepsy										1					
Paraplegia		1		1						2					
Sciatica				1											
Cerebral Tumor	1	1													
Hypochondriasis		1													
Hæmoptysis	3														
Intestinal Hemorrhage								4							
Suppuration		1		1	1										
Cellulitis				1	1		1								
Alcoholism				2			2			1					
Ac. Art. Rheu'sm.		1		8						1					
Chronic Art. "															
Subac. " "				4			2			4					

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